Law and the Public's Health

How the law addresses major policy issues in genetic testing and treatment represents one of the most important issues in public health, science, and law. This installment of *Law and the Public's Health* examines the critical relationship between patent law and genetic testing, as well as the implications of the U.S. Supreme Court's decision on access to genetic tests that can improve health.

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PATENTING GENES: WHAT DOES *ASSOCIATION FOR MOLECULAR PATHOLOGY V. MYRIAD GENETICS* MEAN FOR GENETIC TESTING AND RESEARCH?

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During its 2013 term, the U.S. Supreme Court ruled[1] on a challenge to a patent held on genetic tests for certain genes that increase the risk of breast and ovarian cancer. The patent gave one company a monopoly on a genetic test that involved isolating natural deoxyribonucleic acid (DNA) strands and creating synthetic complementary DNA (cDNA) that mirrored the original isolated strands with slight alterations. The Court ruled that synthetically created cDNA is patentable, while isolated natural DNA is not. This installment of *Law and the Public's Health* examines the Court's decision and its implications for public health.

BACKGROUND

Breast cancer is a leading cause of cancer deaths in women, second only to lung cancer. About 12% of women in the United States will develop breast cancer at some point in their lives, and approximately 3% will die from the disease. During 2013, breast and ovarian cancer claimed the lives of an estimated 53,000 women and resulted in more than 250,000 new diagnoses.[2] In addition to the individual burden of disease and the myriad indirect costs, the direct cost of treating cancer in the U.S. was estimated at $124.6 billion in 2010 (medical care expenditures only), of which the largest share ($16.5 billion) was for the treatment of female breast cancer.[3]

BRCA1 and BRCA2 are genes (i.e., pieces of DNA) that normally help repair damaged DNA. A mutation in one of these genes means that cells are more likely to develop genetic alterations that can lead to cancer. Someone with mutations in the BRCA1 or BRCA2 genes has a significantly higher risk of getting cancer, especially breast, ovarian, and prostate cancer.[4] Mutations in these two genes account for 5%–10% of all breast cancers and about 15% of all ovarian cancers.

Women with mutations in the BRCA1 and/or BRCA2 genes can take steps to mitigate the risk of cancer, including enhanced screening, medications, and preventive surgery to remove breasts and/or ovaries. This prophylactic surgery can significantly reduce the risk of death linked to BRCA mutations.[5]

According to its court filings, Myriad Genetics was the first company to discover the precise location and sequence of the BRCA1 and BRCA2 genes, which allowed it to determine their typical nucleotide sequence.[1] (Myriad's competitors dispute this history, arguing that multiple researchers, many of whom are publicly funded, contributed to the discovery of the locations of BRCA1 and BRCA2.)[6] Based on these discoveries, Myriad developed medical tests to detect BRCA1 and BRCA2 gene mutations, the presence of which would indicate an increased risk of cancer. The tests involved two processes. The first process involved separating segments of DNA containing the sequences of nucleotides (which comprise the "ladder rungs" in the double helix of DNA) typically found in the BRCA1 and BRCA2 gene sequences. The second process involved creating a copy of the original natural DNA sequence that contains only exons (i.e., nucleotides that code for amino acids, the building blocks of proteins), called cDNA.[7]

After it identified the location and sequence of BRCA1 and BRCA2 genes, Myriad obtained a number of patents. The patents covered the act of isolating the genes and the creation of cDNA,[8] giving Myriad exclusive rights to control those processes for 20 years. Although the actions described in the patents are

part of the process of Myriad's BRCA1/2 testing, it is important to note that Myriad's patents did not cover any unique testing methods. When scientists at other institutions began offering BRCA testing after Myriad had discovered the genes, Myriad ordered them to stop, asserting that the testing infringed Myriad's patents. One of the scientists who had been ordered to stop, Dr. Harry Ostrer, sued to declare Myriad's patents invalid, joined by other doctors, patients, and advocacy groups.[8]

Myriad's argument in support of its patents included the following representative claims to patents on the following:

1. "The DNA code that tells a cell to produce the string of BRCA1 amino acids set forth in SEQ ID NO:2 [which identifies 1,864 amino acids found in a typical BRCA1 gene sequence]."
2. "An isolated DNA having at least 15 nucleotides of the DNA of" the above claim.
3. "The cDNA nucleotide sequence listed in SEQ ID No:1, which codes for the typical BRCA1 gene."
4. Isolated cDNA having at least 15 nucleotides of the cDNA sequence in the above claim.[8]

The Federal District Court granted summary judgment to Dr. Ostrer and the other plaintiffs, finding that Myriad's patents were invalid because they covered products of nature.[8] On appeal (after a remand from the Supreme Court to reconsider in light of a recent ruling in another case), the Court of Appeals for the Federal Circuit reversed the lower court, holding that both isolated DNA strands and cDNA may be patented.[9]

The patents claimed by Myriad Genetics would, if upheld, give it the exclusive right to isolate BRCA1 and BRCA2 genes, or any strand of 15 or more nucleotides within them, and the exclusive right to create BRCA cDNA. While asserting these patents to exclude other testing providers, Myriad was the only company that could administer the BRCA1/2 test, for which it charged $3,000–$4,000,[10] yielding a profit of $57 million through June 2013. (Myriad's BRCA1/2 test is currently priced at $4,040.)[11] Immediately after the Supreme Court ruling invalidating some of Myriad's patents, other companies began offering lower-cost BRCA1/2 testing at approximately $1,000–$2,300 per test.[12]

THE COURT'S OPINION

The Supreme Court considered Myriad's claims under the long-held rule that "laws of nature, natural phenomena, and abstract ideas are not patentable," they are the tools of innovation necessary for science and technology. Yet, patents serve to encourage creation by ensuring some degree of profitability. The Supreme Court explained, "Patent protection strikes a delicate balance between creating 'incentives that lead to creation, invention, and discovery' and impeding 'the flow of information that might permit, indeed spur, invention.'" Thus, the question before the Court was whether Myriad's patents pertain to a "new and useful composition of matter" or simply "naturally occurring phenomena."[1] In a unanimous decision, the Court ruled that cDNA is patentable, while segmented, natural DNA is not.

Regarding segmented DNA, the Court explained that, although Myriad "found an important and useful gene, . . . separating that gene from its surrounding genetic material is not an act of invention."[1] Myriad's patents' descriptions explained the iterative process and extensive efforts that led to the identification and isolation of the gene sequences. However, the process of discovery does not necessarily yield a patentable product where the discovered item is naturally occurring. Myriad attempted to argue that the act of severing chemical bonds to isolate the DNA creates a non-naturally occurring molecule. However, the patent asserted by Myriad covered any segment containing the relevant sequence of nucleotides, not a specific molecule with a certain chemical composition.

On the other hand, cDNA is not naturally occurring. In cDNA, "The noncoding regions have been removed."[1] The petitioners argued that, despite this modification, cDNA is not patent-eligible because the sequence of nucleotides is dictated by nature, simply copied into an exons-only version. The Court disagreed, holding that even though the cDNA follows the nucleotide sequence of the natural DNA segment and retains its naturally occurring exons, the cDNA is a new creation and, therefore, patentable.

OUTLOOK AND IMPLICATIONS FOR PUBLIC HEALTH PRACTICE

The implications of the Supreme Court's decision are uncertain. At first glance, it seems to allow more genetic testing providers to offer BRCA1/2 tests, which should make them more widely available and less expensive. Providers other than Myriad will now be able to segment DNA containing the specified nucleotide sequences to search for mutations in the genes. As noted previously, competing testing providers began advertising less expensive BRCA1/2 tests immediately after the Supreme Court's ruling. The decision is expected to increase access and reduce cost for a wide variety of genetic tests, far beyond BRCA1.[13] Increasing

access to BRCA1/2 testing can help women identify an increased risk of cancer earlier so that they can watch their health more closely, have earlier and more frequent screenings (e.g., mammograms), or even choose to have preventive surgery (e.g., prophylactic removal of the breasts and/or ovaries). Health-care providers cheered the decision as a removal of barriers to increase access, reduce costs, and allow for innovation.[12] The Court's decision may also remove barriers in the way of research into new tests and treatments for genetic diseases, as patents on genes have been shown to inhibit genetic research in the past,[14] and researchers will be able to segment natural DNA without worrying about infringing on a patent.

However, the Court upheld Myriad's patent claims with respect to cDNA, so any test that involves the creation of cDNA for BRCA1/2 testing might infringe on Myriad's patents. Again, Myriad's patents do not cover methods, but, rather, patent the cDNA itself. The Court's decision only invalidated five of Myriad's 520 patent claims.[14] Therefore, Myriad may sue any researcher or testing provider that creates the same cDNA independently from an individual's natural DNA, if the cDNA meets the definition outlined in its patent. In fact, shortly after the Supreme Court decision, Myriad sued two competitors that had begun to offer less expensive BRCA1/2 testing for violating its patents.[15] If Myriad is successful in these lawsuits, it will be able to prevent competing providers from offering BRCA1/2 tests, maintaining its monopoly and keeping costs high.

Besides shutting down competitors that may offer less expensive BRCA1/2 tests, the patents Myriad holds may stifle research as well. Could a researcher independently create cDNA containing the series of 15 or more nucleotides described in Myriad's patent from a research subject's natural DNA without violating Myriad's patent? Without the ability to create such cDNA, research may be severely hampered. Krench explained that "unpublished" cDNA (i.e., a cDNA sequence that has not been presented in a conference or research paper) is vulnerable to patent claims by other researchers. She articulated the many questions that remain for genetic researchers after the Supreme Court's decision:

> What if we were to discover that some company has patented the cDNA for the disease we're studying? Would all of our research suddenly be shut down, unless the company agreed to license the cDNA (that my laboratory created, which we already use)? Knowing that our laboratory and thousands of others depend on access to cDNA, should we all stop and file patents to head off opportunistic companies that might try to privatize invaluable research tools? [S]cientists are increasingly turning to artificial DNA synthesis as a research tool. If a machine synthesizes a segment of DNA, but it's the same sequence as a gene found in nature, would that synthesized segment be patentable? What if you changed just a few letters in the DNA sequence, but the resulting protein was unaffected? How many modifications would you have to make to a BRCA1 cDNA sequence before it was different enough not to infringe on Myriad's patent?[7]

These questions illustrate how much remains unclear for scientists and genetic testing providers after the Supreme Court's holding.

Myriad's BRCA1/2 patents are set to expire in 2015, so its monopoly on testing using the patented cDNA is limited. However, the principle articulated by the Supreme Court in the *Myriad Genetics* case surely will be used by other companies to claim patent protection for cDNA used in other types of testing and research. The U.S. Patent and Trademark Office has granted patents on at least 4,000 human genes, and 40% of the human genome is now covered by patents.[16] Some of those patents may be invalidated by the Supreme Court's decision in *Myriad Genetics*, but many others will remain in place, potentially presenting barriers to research and testing for genetic conditions. For individuals who can benefit from genetic testing, the monopolies granted by patent protection for testing and research components such as cDNA may drive up the price of genetic tests and inhibit the evolution of potentially beneficial research, even though the Court invalidated such patents in the case of naturally occurring DNA segments.

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